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Effects of Antihypertensive Drugs on Blood Velocity in Rhesus Monkeys

J. DAVID SPENCE, M.D., F.R.C.P.(C), JAMES PESOUT A.B., AND KENNETH L. MELMON, M.D.

SUMMARY **Increasing evidence suggests that higher blood velocity, by causing turbulence and high shear rates at the endothelial surfaces of arteries, may be important in the pathogenesis of atherosclerosis. In order to measure the effects of antihypertensive agents on blood velocity, an improved method has been developed for analysis of Doppler ultrasound velocity recordings. The audio signal from a Doppler velocity meter is subjected to spectral analysis; the sonagraph thus obtained is digitized with the use of a magnetic table on-line with a calculator. Four monkeys were maintained at a hypertensive baseline for six weeks by infusion of angiotensin and isoproterenol. The effects on blood velocity of 72-hour infusions of propranolol, clonidine, hydralazine, and methyldopa were studied. In doses that reduced diastolic pressure by 13–28%, propranolol *decreased* mean blood velocity (mv) by 17%, clonidine decreased mv by 14%, while methyldopa *increased* mv 12%, and hydralazine increased mv by 52% ($p < .00001$). Antihypertensive drugs appear to have different effects on blood velocity; these differences may influence choice of antihypertensive drugs for the prevention of arterial disease.**

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THEORIES ON the pathogenesis of atherosclerosis cite multiple factors that may initiate and perpetuate the lesions in arterial walls.[1] Various roles might be played by platelets, smooth muscle cells, and lipids in blood.

In 1856,[2] Virchow postulated that mechanical irritation of the intima was the initial event in the process of atherosclerosis. His concepts have been extended in more precise terms such that we now believe these hydromechanical forces at the interface between the circulating blood and the vessel wall, in the form of turbulence and shear stress, may be important pathogenetic factors in atherosclerosis.[3–5] The relative contribution of such forces vis-à-vis the role of platelets, smooth muscle cells, and lipids in the arterial lesions has not been defined.[6]

We now know that treating high blood pressure in some way(s) helps prevent arterial disease. We have, however, given little consideration to the possibility that drugs that lower blood pressure may have differing effects on blood velocity and that these varying actions may contribute to the development of turbulence and shear. No *a priori* reason exists to assume that all drug combinations will offer equal efficacy in the prevention of atherosclerosis, even though they may lower blood pressure to the same degree.

This study develops an experimental approach that might be used in man to test the efficacy of various combinations of antihypertensive drugs in preventing atherosclerosis, and to assign the role played by their effects on blood velocity. We present the methods used to determine blood velocity and preliminary data generated from rhesus monkeys (that were made hypertensive by pharmacologic manipulation) while they received each of four commonly used antihypertensive drugs, at doses sufficient to produce a hypotensive response.

Methods

Animals and Apparatus

Four male monkeys *(Macaca mulatta),* weighing from 4 to 6 kg, were anesthetized with pentobarbital (30 mg/kg). Sterile polyvinyl catheters for infusion of drugs and for recording pressures were inserted into the left iliac artery and vein, tunneled subcutaneously, and brought out through the skin near the umbilicus. Through a vertical incision medial to the left sternocleidomastoid muscle, the left common carotid artery was dissected clear, and the bifurcation into internal and external carotid was identified. A 2 mm periarterial cuff Doppler probe (Parks Electronics, Beaverton, Oregon) was placed around the artery, tied closed, and sutured in place 1 cm below the bifurcation. Care was taken to avoid twisting or compressing the artery. The wires from the Doppler probe were tunneled subcutaneously and brought out through the skin near the umbilicus. Postoperatively the monkeys were placed in primate restraining chairs inside sound-protected isolation booths. The catheters, brought to the outside of the booth, were flushed continuously with lightly heparinized (5 USP units/ml) 0.9%

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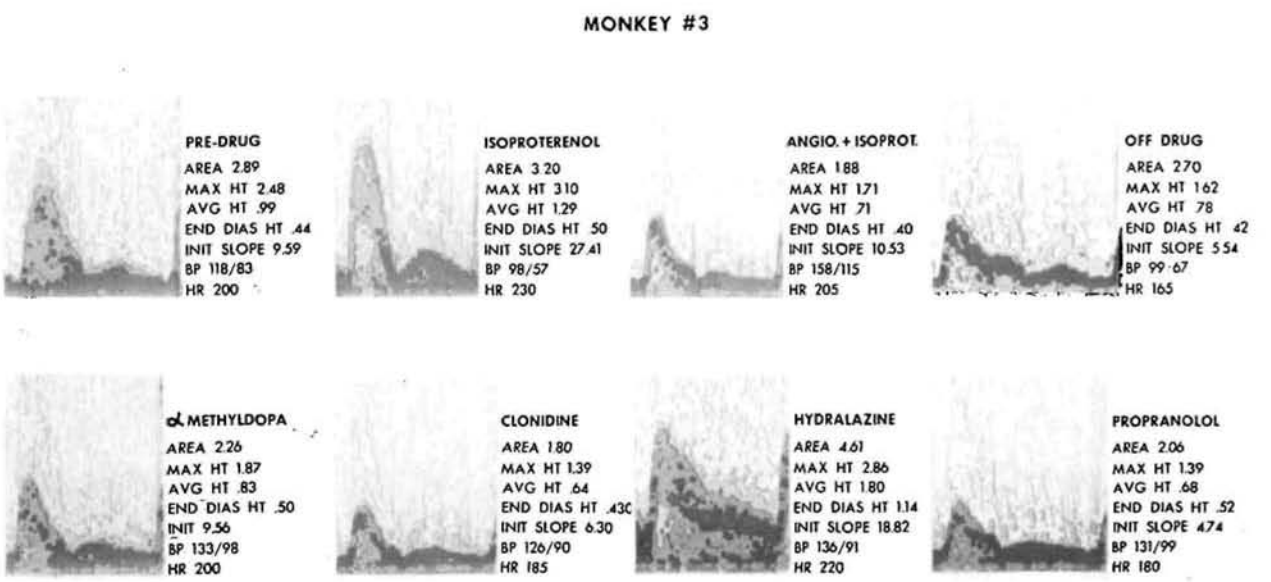

FIGURE 1. *Examples of sonagraphs of Doppler recordings from monkey #3: Before drug, during infusion of isoproterenol, angiotensin and isoproterenol, off drug, and with infusion of methyldopa, clonidine, hydralazine and propranolol, while still on angiotensin and isoproterenol. The waveform measurements obtained from the magnetic digitizer are printed at the right of each waveform. Units of area, maximum height, average height, and end-diastolic height are inches.*

NaCl solution (1.0 ml/hour). All measurements and infusions could be performed without disturbing the monkeys. At least 7 days elapsed before experiments were performed. Pressures from the arterial catheters were measured with Statham P23 GIS transducers, placed at mid-thoracic level. Heart rate was counted from pressure pulse recordings on a Type R Beckman recorder.

Recording of Velocity Waveforms

Blood velocity waveforms were recorded using a Parks Electronics model 806 directional Doppler velocity meter, at a frequency of 9.8 megahertz. This method has been used for a decade.[7-9]

Because of signal averaging, and non-linearity at high frequencies, the zero-cross detector which generates the voltage analogue signal from most Doppler ultrasound velocity meters presents serious problems, which have been discussed in detail by Gosling and others.[9]

For this study, spectral analysis was used to separate noise from waveform and to achieve a linear frequency response. The audio signal from the Doppler velocity meter was recorded with a Sony Dolbyized magnetic tape recorder, and played into a Sonagraph (Kay Elemetrics, Pine Brook, New Jersey). The Sonagraph discretely displays all frequency shifts present in the ultrasound beam at any time on the vertical axis, with time on the horizontal axis. The frequency response is linear in the frequencies used (6Hz–16KHz). Velocity/time waveforms were recorded under a variety of conditions (fig. 1).

Analysis of the Waveforms

A Hewlett-Packard model 9821-A desk-top calculator, with magnetic digitizer, was used to take a number of measurements from the waveforms. The Sonagraph tracings were taped to a magnetic board, and the outer edge of the waveform (maximum frequency envelope) was traced with a magnetic cursor. The calculator read and stored points along the waveform every 0.01 inches. At the end of the tracing, the calculator printed out the following numerical descriptions of the waveform:

Area (inches)	(area under the curve; related to volume of the flow pulse)[11]
Max. ht. (inches)	(peak height; equivalent to peak velocity)[10]
Avg. ht. (inches)	(area under the curve divided by cycle length)[10]
Max./avg. ht.	(ratio of peak height to average height)[10]
Init. slope	(equivalent to rate of rise of velocity with time)
EDH (inches)	(end-diastolic height)

(The program list may be obtained from the author on request.)*

All these measurements were intended to quantitate changes in the velocity waveforms. The physical meaning of the area under a velocity/time waveform is related to the volume of each pulse.[11] Thus the Area (pulse volume) times heart rate (beats per minute) is related to volume flow per minute. In the analysis of the effects of hypotensive drugs, a variable designated as Flow was generated by multiplying Area by heart rate, in the Scattergram program of the Statistical Package for Social Sciences (SPSS),[12] run on an IBM 360/50 computer. The remaining velocity variables used for analysis were measurements, in inches, taken from the Sonagrams by the calculator-digitizer.

*The author is indebted to Dr. Jon Goerke for assistance with this program.

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TABLE 1 *Baseline Observations for Three Monkeys (mean ± SEM). N = 8 for Each Monkey (on Angiotension and Isoproterenol).*

	Monkey 1	Monkey 2	Monkey 3
Variable			
Heart rate (beats/min)	195 ± 4.9	212.5 ± 5.5	205.6 ± 3.3
Systolic pressure (mm Hg)	154.5 ± 2.4	159.9 ± 2.1	156.5 ± 1.8
Diastolic pressure (mm Hg)	113.4 ± 2.0	114.5 ± 1.9	112.5 ± 2.8
Area (inches)	3.5 ± .29	3.7 ± .23	2.4 ± .19
Maximum height (inches)	2.2 ± .09	2.7 ± .08	1.8 ± .07
Average height (inches)	1.2 ± .12	1.4 ± .1	.86 ± .05
End-diastolic height (inches)	.80 ± .11	.91 ± .08	.52 ± .06
Slope	8.8 ± .46	13.49 ± 1.1	9.2 ± 1.1

Accuracy

The variability (coefficient of variation) in repeated tracings of the same waveform was less than two percent for all measurements except slope. The slope, which was calculated from the angle between the baseline and the leading edge of the waveform, was very sensitive to slight errors in tracing because the slope was so steep. The variability in repeated tracings of steep slopes was 10 to 12%. For this reason, waveforms were traced in triplicate and the measurements averaged. The variation between successive waveforms in the recordings did not exceed the variation in repeated tracings of single waveforms.

The methods used for recording and analyzing velocity waveforms were adapted from Gosling and King.[9] The modifications were: (1) the use of a periarterial cuff Doppler probe for animal work, (2) the use of the contour display, (3) digitization was in x and y, with sampling of the waveform every 0.01 inches. This meant that about a thousand points were plotted and used by the calculator to estimate slope, area, peak height, and other dimensions, giving an accurate result that was printed out directly on line with the digitizer. This method was not only more convenient, but gave more numerical descriptions of the waveform, with greater precision, than the unmodified method, which used IBM punch cards to calculate peak height: average height ratios from a digitization in y of only 100 points along the waveform.

Experimental Protocol for Study of Hypotensive Drugs

We developed an animal model that had reliable and steady increases in both cardiac output and peripheral resistance. Isoproterenol was used to increase cardiac output, and angiotensin was used to increase peripheral resistance. Although isoproterenol alone caused major increases in peak velocity, acceleration, pulsatility (maximum height/average height ratio) and cardiac output, the addition of angiotensin to the regimen largely reversed these changes, even though the isoproterenol was still being infused (see fig. 1).

Drug Doses Used to Produce Hypertension

A dose of isoproterenol that would increase heart rate 20% was determined experimentally. Then a dose of angiotensin (Hypertensin®) that caused a 40% increase over basal blood pressure was added. The doses used were 20 μg/kg/hour (isoproterenol) and 5 mcg/kg/hour (angiotensin). A stable hypertensive state was reached within 36 hours after the start of the combined angiotensin/isoproterenol infusion. At the end of the study all drugs, including angiotensin and isoproterenol, were stopped; the monkeys returned to their pre-drug baseline levels of blood pressure, heart rate, and blood velocity within three or four days.

Hypotensive Drugs

Each antihypertensive drug was given using at least three infusion rates, continuing each infusion for 24 hours. In addition, to obtain greater effects, a bolus of hypotensive drug was given at the beginning of each new infusion period.

At least three days elapsed between infusions of antihypertensive drugs; no new drug was started until the monkey's heart rate and blood pressure returned to baseline; a randomized latin square assignment of drug sequences was used to minimize further the effect of carryout of drug from one period to the next. Each monkey received all four hypotensive drugs, so that effects of each drug were compared with each monkey's own hypertensive baseline, which was taken to be the mean of eight observations obtained before and after each 72-hour experimental period in which a hypotensive drug was given. The baseline was stable for each monkey (table 1), suggesting the ambient conditions of lighting, sound protection, temperature, feeding, and contact with study personnel were adequately controlled and did not interfere with measurements.

Hypotensive Drug Doses

Daily boluses of clonidine (Catapres®)* 20 mcg/kg were followed by 24-hour infusions at a rate of 5 mcg/kg/hour, 10 mcg/kg/hour, and 15 mcg/kg/hour. After 3 days, the hypotensive effect of clonidine diminished, but the effect on heart rate persisted. Because a hypotensive effect was desired, an infusion of 20 mcg/kg/hour was given for an additional 24 hours, without a preceding bolus, to all four monkeys. Hypotension occurred at this last dose, and the monkeys became drowsy. Hydralazine (Apresoline®) was given daily for three days as a bolus of 200 mcg/kg, followed by infusions for 24 hours each at the rate of 50 mcg/kg/hour, 75 mcg/kg/hour, and 100 mcg/kg/hour. Boluses of propranolol (Inderal®) were 100 mcg/kg, and infusions were at the rate of 10, 20, and 40 mcg/kg/hour. These doses were all chosen in pilot studies done to determine doses that would produce a hypotensive response without causing dangerous hypotension and bradycardia.

*Kindly supplied by Boehringer Ingelheim Ltd.

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Timing of Measurements

Heart rate, blood pressure, and Doppler velocity recordings were sampled at 15 minutes, and at 1, 3, and 24 hours after each bolus-infusion sequence was started. These times were chosen to take advantage of both the rapid changes following the bolus, and the relatively steady state at the end of each 24-hour infusion.

The Doppler velocity meter gives essentially the same velocity/time waveform as an electromagnetic flowmeter,[7] and the parent method of Gosling and King[9] has been used in humans to assess peripheral vascular disease.

Results

All monkeys experienced similar effects from the angiotensin and isoproterenol; their blood pressures increased from 105–115/55–65 to 150–160/105–120, and their heart rates went from 165–175 per minute to 195–205 per minute. Baseline observations were made for each monkey in duplicate 30 minutes apart on eight occasions, before starting on hypotensive drugs, and, after each hypotensive drug was given, before starting the next drug. The mean of all baseline observations for each monkey was determined, and all changes caused by hypotensive drugs were taken as a percent change from each monkey's own mean baseline. The use of a mean baseline minimized carryover effect of drugs; percent changes were calculated in order to normalize all of the variables to similar orders of magnitude (the waveform measurements, in inches and square inches, were numerically much smaller than the pressure and rate measurements).

Effects of Antihypertensive Agents

Mean changes in diastolic pressure, velocity (maximum, average, and end-diastolic waveform height), and acceleration (initial slope of waveform) are shown in figure 2.

We placed the drugs studied into two groups, based on their effect on blood velocity waveforms. Propranolol and clonidine decreased, while hydralazine and methyldopa increased, blood velocity. However, clonidine and methyldopa affected acceleration in a paradoxical manner. Clonidine caused an increase, while methyldopa caused a decrease, in acceleration (when considered in relation to a decrease in blood pressure). However, the relationships appear to support the distinction between propranolol and clonidine as drugs that decrease velocity, and hydralazine and methyldopa as drugs that increase velocity. When the changes in peak velocity and acceleration were examined in relation to flow, both propranolol and clonidine decreased acceleration, peak velocity, and flow, while methyldopa and hydralazine increased all these variables.

Statistical Analysis

Because some of the changes in velocity and acceleration may have been confounded by associated changes in heart rate or flow, the relationships between the variables were examined by partial correlation analysis. Calculations were done on an IBM 360/50 computer, and the subprogram Partial Correlation of the Statistical Package for the Social Sciences (SPSS)[12] was used. The observations that were made at the times when the diastolic pressure was increased above baseline were excluded from consideration because the object of the study was to examine the changes in blood velocity that occur when hypotension is seen.

Analysis of covariance showed that, rather than accounting for the association between changes in peak velocity and acceleration and changes in pressure, heart rate and blood flow were actually obscuring the relationship. Similarly, correlations between changes in peak velocity and flow, and between acceleration and flow were increased by controlling for covariance in heart rate and pressure. Correlations between velocity parameters and systolic pressure were increased by controlling for covariance in diastolic pressure and heart rate. (Partial correlation tables may be obtained from the author on request.) In no case did this analysis indicate that the relationships were accounted for by

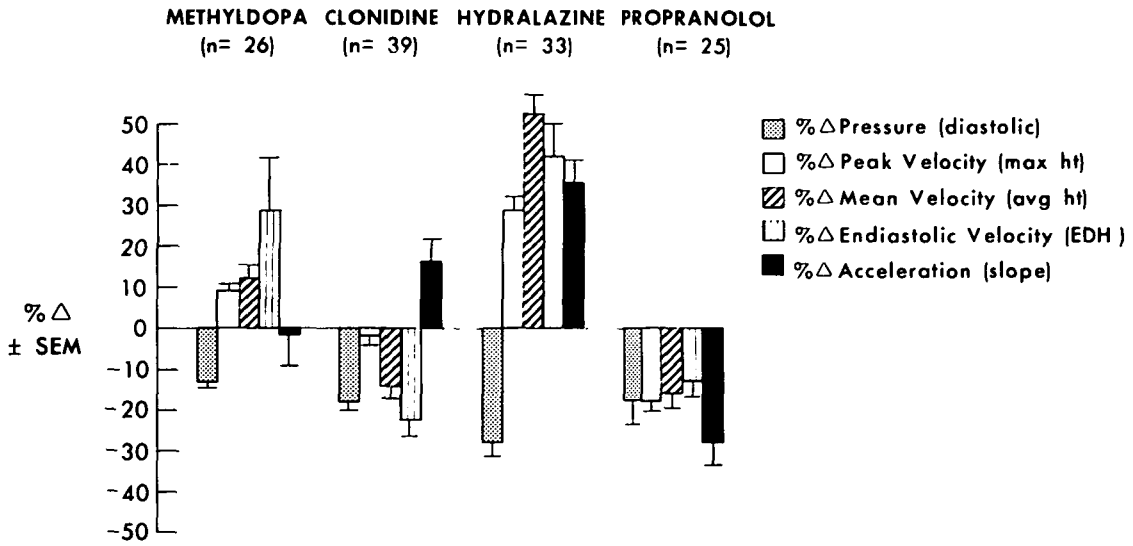

FIGURE 2. *Percent change from mean baseline (±SEM) of blood pressure, peak velocity, mean velocity, end-diastolic velocity, and systolic acceleration. Mean of 3 monkeys; all observations during hypotensive effect of drugs.*

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covariance of any other variable measured.

Differences between the effects of the hypotensive drugs on blood velocity were studied by constructing a two-by-four contingency table for each of the variables: slope, average height, end-diastolic height, maximum height, and flow. The four columns represented the four drugs; the two rows represented an increase or decrease of the parameter of velocity relative to baseline for all cases in which diastolic pressure was below baseline. Chi-square was computed with the use of subprogram Crosstabs of SPSS.[12] The effects of the four hypotensive drugs were significantly different for all five parameters of velocity ($p < .00001$).

Discussion

Diastolic hypertension is commonly treated with drugs that lower blood pressure, in the belief that the treatment will prevent vascular disease. Indeed, congestive heart failure and hypertensive arteriolar disease of the brain and kidneys probably are prevented by treatment.[13-15] Strokes are prevented when blood pressure is lowered, but two investigators[16, 17] have recently suggested that the strokes that are prevented are the manifestations of *arteriolar* disease, such as lacunar infarction or hemorrhage from cerebral microaneurysms; brain infarcts from *arterial* occlusive disease are less likely to be prevented by lowering blood pressure. A parallel observation is that *arterial* disease, manifested as myocardial infarction, is equally common in both well-controlled and poorly controlled hypertensives.[13-15]

Because hypertension is widely recognized as a risk factor for atherosclerosis, these observations seem paradoxical. However, the Framingham study showed that systolic hypertension correlates more strongly with risk of coronary artery disease than does diastolic hypertension.[18]

These observations are consistent with the possibility that some force associated with hypertension, but distinct from increased pressure, might be related to the pathogenesis of atherosclerosis. This conjecture is supported by some biophysical calculations, pathological observations, and experimental data: the lesions of atherosclerosis do not occur evenly throughout the vascular tree, but are localized to branches and bends.[3, 19]

Under normal conditions, the endothelial surface of blood vessels is protected from rapidly moving blood by laminar flow: Blood near the vessel wall moves slowly, while faster-moving blood is in the center of the vessel. At high velocities, and particularly at bends and bifurcations, flow can become non-laminar with the development of turbulence and high velocity gradients.[20] The localization of atheroma at bifurcations has led to the suggestion that disturbance of flow at bifurcations results in endothelial damage, which initiates the atherosclerotic process.[2, 4] Fry and others have shown that high shear rates and turbulence are capable of damaging endothelium, while, in the same study, areas of peak pressure stress were not the site of localized endothelial damage.[21]

Ross *et al.* have recently demonstrated the roles of endothelial damage, platelets, smooth muscle cells, and hyperlipidemia in the initiation and maintenance of atherosclerotic lesions.[22, 23]

Turbulence, defined as the chaotic flow pattern that develops when flow becomes non-laminar, causes pressure energy to be converted to kinetic energy, and results in loss of energy (heat and vibration) into the vessel wall.[24]

Although acceleration and a frequency factor may be important to the transition from laminar flow to a turbulent state *in vitro*, the importance of these factors to flow in arteries is uncertain.[25] For steady flow, the development of turbulence is predicted by the critical velocity at which the dimensionless Reynolds number exceeds a critical level. Roach *et al.* showed that the velocity required to produce turbulence is lower with pulsatile flow, and with increasing angle of bifurcation.[26] Blood velocity is the most important characteristic of the circulation that determines whether turbulence will occur at bifurcations.[26]

We believe this justifies an interest in the hypothesis that, in order to prevent disease of *arteries*, as opposed to disease of *arterioles*, the treatment of hypertension might take into account alterations in the blood velocity. If all antihypertensive agents were found to lower blood velocity to the same degree that they lower pressure, then selection among these drugs would be inconsequential.

The velocity of blood in a vessel can be determined by dividing flow by the cross-sectional area of the vessel. Assuming that there are no major changes in the diameter of major blood vessels, mean velocity in the aorta and its branches is a function of cardiac output. Thus, propranolol, which decreases cardiac output, would be expected to decrease mean velocity, whereas hydralazine, which is a vasodilator and causes increased cardiac output, would be expected to increase mean velocity. It was not an unexpected finding that propranolol, which causes decreased rate of ejection of blood from the heart, decreased the systolic acceleration and peak velocity of blood leaving the heart. What was striking, however, was the segregation of the effects on systolic acceleration from the effects on velocity, which was observed with clonidine and methyldopa.

The observations presented here might add one more point of justification for comparative studies of overall efficacy between various combinations of drugs, based on their effects on blood velocity. If peak velocity and mean velocity were the main determinants of hemodynamic disturbance, then our observations suggest that propranolol and clonidine, as drugs that decrease velocity, might be contrasted with hydralazine and methyldopa, as drugs that increase velocity. The effect of combining propranolol with vasodilators would be of interest.

Studies of the differential effects of drugs that lower velocity from those that do not, and the effects of these commonly used drugs on sustained changes in velocity, are justified and can be accomplished. Non-invasive methods for obtaining blood velocity tracings, such as the Doppler method used here, may make it possible to verify the effects of drugs on patients over the long periods that are required to observe changes in human arterial disease.

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Cervical Manipulation and Stroke

J. DONALD EASTON, M.D. AND DAVID G. SHERMAN, M.D.

SUMMARY Three patients are described who experienced vertebro-basilar distribution infarctions associated with neck manipulation. Two of the manipulations were chiropractic. Twenty-two previously reported cases are reviewed. Evidence favoring the use of anticoagulation in these patients is discussed along with the relative risk of such therapy.

INFARCTION of the brain or spinal cord has resulted from a variety of conditions producing injury to the vertebral arteries. These infarctions have been associated with non-fusion of the odontoid with atlantoaxial subluxation,[1, 2] cervical osteoarthritis,[3, 4] fracture or dislocation of the cervical spine, seemingly minor falls without cervical injury,[5] and hyperextension of the neck associated with athletic activities or work.[6, 7]

Chiropractic manipulations of the neck may also produce brain infarction.[8-19] Miller and Burton[17] emphasized that patients with cervical spondylosis or vertebro-basilar insufficiency should not undergo chiropractic manipulation and that it should be terminated immediately in any patient who develops ischemic symptoms.

Many patients have progression of the ischemic symptoms over hours or days. Angiograms have demonstrated vertebral artery narrowing and the brain pathology has shown vertebro-basilar distribution infarction. For these reasons, immediate anticoagulation seems reasonable, and some authors consider it the treatment of choice.[18]

This report describes three patients who developed brainstem and/or cerebellar infarction after neck manipulation. Two of them underwent chiropractic manipulation and one a spontaneous head turn. One patient was heparinized because the stroke was progressing and autopsy showed a large hemorrhagic infarction of the pons, medulla and cerebellum.

Case 1

A 38-year-old woman turned her head to look behind her while driving and experienced severe pain in the right occipital area with momentary total visual loss. The headache persisted and three days later she developed vertigo, blurred vision, ataxia, dysarthria and dysphagia.

Physical examination showed an alert, dysarthric woman with right occipital headache. The right pupil was miotic and there was rotary and horizontal nystagmus with diplopia on rightward gaze. Right facial sensation was diminished and

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